Clinical utility of tubular markers in kidney disease: a narrative review

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Background and Objective: Various tubular markers have been established for the diagnosis of kidney diseases and evaluation of treatment efficacy. Currently, there are limited treatments available for advanced kidney disease. Therefore, early identification of patients at high risk of progression to end-stage renal disease (ESRD) is necessary for the provision of appropriate treatment at an early phase. The present review focuses on newly established urinary tubular markers, i.e., urinary [tissue inhibitor of metalloproteinases-2 (TIMP-2)]*[insulin-like growth factor binding protein-7 (IGFBP7)] and L-type fatty acid binding protein (L-FABP).

Methods: A literature search of the electronic databases MEDLINE (January 2014 to February 2022) was conducted using search terms of "urinary [TIMP-2]*[IGFBP7]", "urinary L-FABP", "kidney disease", and "COVID-19". Original articles, which were written in English and show clinical usefulness of urinary [TIMP-2]*[IGFBP7] or urinary L-FABP, were mainly reviewed.

Key Content and Findings: These proteins are expressed in human tubules and are reported to have renoprotective functions against kidney disease. In 2014, the U.S. Food and Drug Administration approved the clinical application of NephroCheck, measuring urinary [TIMP-2]*[IGFBP7], for the diagnosis of acute kidney injury (AKI). Notably, the usefulness of urinary L-FABP in AKI, chronic kidney disease (CKD), diabetic kidney disease, aging, and coronavirus disease 2019 (COVID-19) has been widely reported. Furthermore, various methods have been established for the easy, rapid, and highly sensitive measurements of c in various situations. In 2011, urinary L-FABP was approved by the Ministry of Health, Labor and Welfare in Japan.

Conclusions: Early utilization of an accurate marker may improve the prognosis of kidney disease and patient survival.

Keywords: Acute kidney injury (AKI); chronic kidney disease (CKD); tubular marker; [tissue inhibitor of metalloproteinases-2]*[insulin-like growth factor binding protein-7] ([TIMP-2]*[IGFBP7]); L-type fatty acid binding protein (L-FABP)

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Introduction

Owing to the aging of the population, the number of patients with chronic kidney disease (CKD) is increasing (1). Kidney function gradually declines with advancing age due to deterioration of the nephron, which is the functional unit of the kidney (2,3). Furthermore, reduced kidney function is associated with a high risk for the onset of cardiovascular events (4,5). Consequently, aggressive medical interventions

Table 1 Molecules of TIMP-2, IGFBP7, and L-FABP

Characteristics	TIMP-2	IGFBP7	L-FABP
Molecule weight	24 kDa	29 kDa	14 kDa
Expression tubules in human kidney	Distal tubules	Proximal tubules	Proximal tubules
Related function	Cell cycle arrest	Cell cycle arrest	Fatty metabolism
			Scavenging of reactive oxygen species
Measuring method	NephroCheck		ELISA
			LTIA
			POC assay kit
Clinical utility in kidney disease	AKI		AKI and CKD

TIMP-2, tissue inhibitor of metalloproteinases-2; IGFBP7, insulin-like growth factor binding protein-7; L-FABP, L-type fatty acid binding protein; ELISA, enzyme-linked immunosorbent assay; LTIA, latex-enhanced immunoturbidimetric assay; POC, point-of-care; AKI, acute kidney injury; CKD, chronic kidney disease.

are required following the development of such events. Nevertheless, these interventions occasionally lead to the occurrence of acute kidney injury (AKI) owing to renal ischemia or the use of contrast media (6-8). Severe kidney disease can easily progress to end-stage renal disease (ESRD), requiring renal replacement therapy (i.e., hemodialysis, continuous ambulatory peritoneal dialysis) and renal transplantation. In addition, there is a well-established association between kidney dysfunction and heart failure, which is termed "Cardiorenal syndrome" (9,10). However, currently, there is a limited number of novel treatments against severe kidney disease. Therefore, early diagnosis of kidney disease and identification of patients at high risk of kidney disease progression are warranted for the administration of appropriate treatments at an early phase.

Serum creatinine is widely used as a marker for the evaluation of kidney function. However, change in serum creatinine levels is slow; thereby delaying the early diagnosis and intervention, particularly in AKI (11-13). Therefore, additional useful markers are required in clinical practice. The degree of tubulointerstitial damage is strongly associated with poor renal prognosis versus that of glomerular damage. Hence, the marker which accurately reflects pathophysiological changes in the tubulointerstitium is useful for providing appropriate treatment to the patients with kidney disease. Recently, new urinary tubular markers were established, and their clinical utility was widely investigated in AKI and CKD induced by various causes. This review focuses on newly established urinary tubular markers, namely urinary [tissue inhibitor of metalloproteinases-2 (TIMP-2)]*[insulin-like growth factor binding protein-7 (IGFBP7)] and L-type fatty acid binding protein (L-FABP) were focused (*Table 1*). We present the following article in accordance with the Narrative Review reporting checklist (available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-22-24/rc).

Methods

A literature search of the electronic databases MEDLINE (January 2014 to February 2022) was conducted using search terms of "urinary [TIMP-2]*[IGFBP7]", "urinary L-FABP", "kidney disease", and "COVID-19". Original articles, which were written in English and show clinical usefulness of urinary [TIMP-2]*[IGFBP7] or urinary L-FABP, were mainly reviewed.

Discussion

Urinary [TIMP-2][IGFBP7] as a marker of AKI*

In human kidneys, TIMP-2 is expressed mostly in distal tubules, while IGFBP7 is expressed in proximal tubules (14). Both TIMP-2 and IGFBP7 are related to cell cycle arrest. A recent study indicated that increased glomerular filtration or decreased tubular reabsorption may be the mechanism underlying the increase in urinary [TIMP-2]*[IGFBP7] in AKI (15); moreover, upregulation of TIMP-2 and IGFBP7 in response to tubular stress, leading to increased urinary excretion, has been reported (16).

Urinary [TIMP-2]*[IGFBP7] is useful for the early

diagnosis of AKI and prediction of disease severity (17,18). In 2014, the U.S. Food and Drug Administration approved the clinical application of NephroCheck, measuring urinary [TIMP-2]*[IGFBP7], for the diagnosis of AKI. A study in adult patients at the intensive care unit (ICU), analyzing urinary samples collected within 18h of study enrollment, demonstrated that urinary [TIMP-2]*[IGFBP7] predicts the onset of severe AKI, sustained kidney dysfunction, or death within 30 days (18). The proposed cut-off value of urinary [TIMP-2]*[IGFBP7] for AKI was proposed as 0.3 $(ng/mL)^2/1,000$ (19,20). Furthermore, in the patients at higher risk of AKI determined using NephroCheck, treatment for AKI according to the Kidney Disease: Improving Global Outcomes guidelines prior to intervention prevented the onset of cardiac surgery-associated AKI. However, this approach did not improve the survival rate (21). It has been shown that urinary [TIMP-2]*[IGFBP7] for the prediction of AKI is not useful in aortic surgery and orthotopic liver transplantation, apart from cardiac surgery (22,23). Regarding the occurrence of AKI after emergency laparotomy in patients with sepsis, research has revealed that there were no significant differences in urinary [TIMP-2]*[IGFBP7] between the AKI and non-AKI groups (24). At present, the usefulness of urinary [TIMP-2]*[IGFBP7] for the diagnosis of AKI induced by various causes remains to be determined.

Urinary L-FABP as a marker of AKI and CKD

L-FABP, which has a molecular weight of 14 kDa, is expressed in human proximal tubules. L-FABP is not expressed in murine kidneys. Hence, the dynamics of renal L-FABP in various kidney diseases have been assessed in numerous experimental studies using human L-FABP chromosomal transgenic mice because (25). Renal L-FABP expression was consistently upregulated and the urinary excretion of L-FABP was increased in different renal experimental models (25). L-FABP has a renoprotective function by accelerating the fatty metabolism and scavenging of reactive oxygen species (25). In human renal tissues obtained through renal biopsy, the levels of urinary L-FABP were significantly correlated with the degree of tubulointerstitial damage (26,27); therefore, urinary L-FABP is considered to be a tubular marker. The clinical usefulness of urinary L-FABP in various kidney diseases has been demonstrated in studies performed worldwide. Of note, in 2011, the measurement of urinary L-FABP in both AKI and CKD was approved by the Ministry of Health, Labor and Welfare in Japan. We previously reviewed the relationship between urinary L-FABP and kidney disease (28-30). In the present review, we discuss recent evidence regarding urinary L-FABP (*Table 2*).

Characteristics of urinary L-FABP

Renal hypoxia is a risk factor for the progression of kidney disease (43). Yamamoto *et al.* investigated the relationship between renal hypoxia and urinary L-FABP. Using an intravital video charge-coupled device, they reported that the urinary levels of L-FABP were significantly decreased following an increase in renal peritubular capillary blood flow in a recipient of a living-related kidney transplant; however, the levels of urinary N-acetyl-β-d-glucosaminidase, α1-microglobulin, and β2-microglobulin were not decreased (44). In addition, we reported that the levels of urinary L-FABP showed a significant negative correlation with the degree of renal peritubular capillary blood flow, measured by diffuse correlation spectroscopy in experimental models of type 2 diabetes (45). Furthermore, renal hypoxia is induced by anemia, which decreases the delivery of oxygen to tissues. Urinary L-FABP levels increased with the progression of anemia in type 2 diabetes (46) and were significantly correlated with the degree of anemia (47). According to these studies, apart from other markers, urinary L-FABP may reflect the degree of renal hypoxia.

Hypoxia-inducible factor-1α (HIF-1α) is upregulated by renal hypoxia in proximal tubules and binds to HIF-1α-binding sites which exist in the promotor region of target genes, leading to the upregulation of those genes (48). As L-FABP has HIF-1α binding sites in its promoter region, renal hypoxia may upregulate the expression of renal L-FABP and accelerate its urinary excretion (49). Therefore, urinary L-FABP may reflect renal microcirculation. From this perspective, urinary L-FABP may be superior to other markers.

Measurements of urinary L-FABP

To measure urinary L-FABP, monoclonal antibodies against human L-FABP were produced and a two-step sandwich enzyme-linked immunosorbent assay (ELISA) was established (50,51). Thereafter, a latex-enhanced immunoturbidimetric assay was developed for the simple, rapid, and highly sensitive (similar to ELISA) measurement of urinary L-FABP (52). Furthermore, a highly sensitive urinary L-FABP kit (39) and a point-of-care (POC) assay kit (31) for the qualitative analysis of urinary L-FABP were

Table 2 Summary of urinary L-FABP in recent studies (from 2016 to 2022) focused on the present review

Disease	Type of clinical study	Situation	Clinical utility	Reference number	Year
AKI	Prospective and single center study	Sepsis	Prediction of sepsis severity	(31)	2017
	Meta-analysis	Different situations (e.g., ICU, surgery, and injection of contrast media)	Prediction of AKI	(32)	2022
	Prospective and single center study	OSR of an abdominal aortic aneurysm	Prediction of AKI	(33)	2021
			Different cut-off levels of urinary L-FABP for predicting AKI according to the position of AXC		
	Prospective and single center study	Emergency laparotomy for acute abdomen by disease of the digestive system	Prediction of AKI	(24)	2022
	In silico study using CPV®	Percutaneous cardiovascular interventions	Prediction of CI-AKI	(34)	2022
AKI to CKD	Prospective and single center study	OSR of an abdominal aortic aneurysm	Prediction of chronic renal dysfunction after AKI	(33)	2021
	Prospective and single center study	Non-surgical cardiac ICUs	Prediction of all-cause mortality or progression to ESRD after AKI	(35)	2020
CKD	Prospective and multicenter study	CKD with and without type 2 diabetes	Prediction of cardiovascular event and ESRD	(36)	2016
	Prospective and single center study	Type 1 diabetes without albuminuria	Prediction of mortality and stroke	(37)	2017
	Prospective and single center study	Hypertension	Prediction of cardiovascular morbidity and mortality, and progression of CKD	(38)	2020
Aging	Prospective and single center study	Healthy adults without CKD	Possibility of reflecting the degree of age-related nephrosclerosis	(39,40)	2017, 2018
COVID-19	Prospective and single center study	COVID-19	Prediction of COVID-19 severity	(41)	2021
	Prospective and single center study	COVID-19	Prediction of COVID-19 severity	(42)	2020

L-FABP, L-type fatty acid binding protein; AKI, acute kidney injury; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; CPV®, Clinical Performance and Value; ICU, intensive care unit; OSR, open surgical repair; AXC, aortic cross-clamping; CI-AKI, contrast media-induced AKI; ESRD, end-stage renal disease.

recently established. The urinary POC kit offers simple measurements for early diagnosis and intervention.

Urinary L-FABP in AKI

Recently, a meta-analysis was conducted on the clinical utility of urinary (n=25 studies) and plasma (n=2 studies) L-FABP for predicting AKI (32). The estimated sensitivity [0.74, 95% confidence interval (CI): 0.69–0.80)], specificity (0.78, 95% CI: 0.71–0.83), and the area under the receiver operating curve (0.82, 95% CI: 0.79–0.85) of L-FABP suggested that it is a reliable marker with moderate accuracy for predicting AKI in different situations (e.g., ICU, surgery, and injection of contrast media). The cut-off levels of urinary L-FABP for the prediction of AKI varied in clinical studies because the cause of AKI is heterogenous and the invasiveness in each type of surgery differs. In patients undergoing open surgical repair (OSR) of an abdominal aortic aneurysm, the cut-off levels of urinary L-FABP for predicting AKI differed according to the position of aortic cross-clamping (AXC) (33). Urinary L-FABP increased to maximum levels at 2 h after AXC, regardless of the occurrence of AKI. Nonetheless, the levels of urinary L-FABP at 2 h after AXC were significantly greater in patients who underwent suprarenal AXC than in those who underwent infrarenal AXC. This is because the suprarenal AXC induced renal hypoxia more strongly compared with the infrarenal AXC (33). Therefore, the cut-off levels of urinary L-FABP for predicting AKI were significantly higher in patients undergoing suprarenal AXC than in those with infrarenal AXC (33). The evaluation of urinary L-FABP levels in clinical practice should be adapted according to the cause of AKI and type of surgery.

In addition, AKI is a risk factor for CKD and ESRD (53,54), and is related to mortality (55,56). Therefore, the relationship between urinary L-FABP and adverse outcomes in the chronic phase of kidney disease after AKI has been investigated. In patients with onset of AKI who underwent OSR of an abdominal aortic aneurysm, the levels of urinary

L-FABP at 2 h after AXC were significantly correlated with reductions in estimated glomerular filtration rate at 3 years after surgery (33). In another study with an observation period of 41 months (n=1,119), involving a heterogenous cohort of patients treated at non-surgical cardiac ICUs, urinary L-FABP on admission was an independent predictor for the primary endpoint, namely all-cause mortality (n=228, approximately 60% cardiovascular deaths) or progression to ESRD (n=17) (35). In addition to creatine-defined AKI, measurement of urinary L-FABP was useful for the identification of patients at high risk for the primary endpoint.

The POC kit of urinary L-FABP may be useful for the early prediction of AKI in clinical practice. A study investigated patients (n=48) who underwent emergency laparotomy for acute abdomen by disease of the digestive system. The qualitative analysis of L-FABP for the prediction of AKI during the perioperative period showed perfect specificity (100%) before the operation and high specificity (>91.9%) at 2, 24, 48, and 72 h after the operation; however, it showed lower sensitivity (24). The L-FABP POC kit may be useful for the discrimination of patients at low risk of AKI. Furthermore, research has demonstrated the clinical usefulness of the L-FABP POC kit for the prediction of contrast media-induced AKI (CI-AKI) in percutaneous cardiovascular interventions (34). CI-AKI is a major cause of AKI in the hospital setting. An *in silico* study using Clinical Performance and Value (CPV®) vignettes showed that cardiologists were able to correctly identify the patients at high risk of CI-AKI using the L-FABP POC kit (34).

Urinary L-FABP in CKD

Urinary L-FABP is a useful tubular marker for the identification of patients at high risk of CKD progression (28-30). In our previous multicenter trial involving non-diabetic patients with CKD, urinary L-FABP exhibited higher sensitivity for predicting the progression of CKD compared with urinary albumin (51). In addition, these results were corroborated by finding in patients with diabetic nephropathy (DN) (57). DN is a main cause of progression to ESRD. Hence, the detection of the patients at high risk of progression to ESRD is necessary for the administration of effective treatments at an early stage of DN (58). In the stage of normoalbuminuria, urinary L-FABP levels were significantly higher in patients with diabetes versus healthy controls (57,59). Moreover, higher level of urinary L-FABP was an independent risk factor for the progression of DN (28,30).

Furthermore, it is well established that CKD can be easily complicated by the onset of cardiovascular diseases (4). In clinical practice, it is necessary to consider measures for the prevention of cardiovascular events in addition to the management of CKD. Therefore, the relationships between urinary L-FABP and the onset of cardiovascular events in patients with CKD were investigated (36,60). Our multicenter trial with an observation period of approximately 3.8 years (n=244) showed that higher level of urinary L-FABP was an independent risk factor for the primary endpoint, defined as the onset of a cardiovascular event or progression of ESRD [higher urinary L-FABP, hazard ratio (HR): 1.34] (36). A study involving type 1 diabetic patients without albuminuria showed that urinary L-FABP was associated with the onset of stroke (37). Furthermore, a 5-year follow-up study of patients with non-diabetic hypertension (n=197) showed that urinary L-FABP was able to predict cardiovascular morbidity and mortality (higher urinary L-FABP, HR: 1.21), as well as progression of CKD (higher urinary L-FABP, HR: 1.19) (38).

Urinary L-FABP in aging

Healthy aging is associated with changes in both renal macrostructure and microstructure caused by renal arteriosclerosis/arteriolosclerosis, which is defined as fibrous thickening or hyalinosis of the vascular intima (3,61). It is thought that renal arteriosclerosis/arteriolosclerosis is considered to provoke renal ischemia or hypoxia, leading to glomerulosclerosis, tubular atrophy, and interstitial fibrosis. Such renal pathological changes are referred to as nephrosclerosis and are related to a decrease in renal function. In older adults with age-related nephrosclerosis, hypertension or other relevant comorbidities can easily cause kidney disease, thereby increasing the risk of ESRD (3). Therefore, evaluation of the degree of age-related nephrosclerosis and appropriate management strategies against nephrosclerosis may contribute to the prevention of progression to ESRD and prolong the healthy life expectancy in older adults. However, monitoring markers for age-related nephrosclerosis have not been established yet.

Kosaki *et al.* reported that the levels of urinary L-FABP in healthy adults without CKD increased along with aging, but remained within the normal reference range (39). Furthermore, they showed that urinary L-FABP levels were negatively correlated with physical capacity, evaluated by maximal oxygen consumption and grip strength. It was

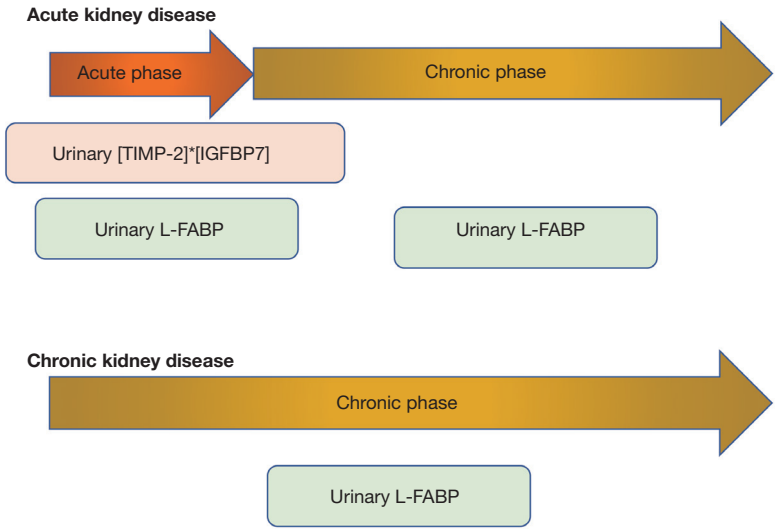

Figure 1 Clinical utility of urinary [TIMP-2]*[IGFBP7] and L-FABP in kidney diseases. While urinary [TIMP-2]*[IGFBP7] is measured for AKI, urinary L-FABP for AKI, AKI to CKD, and CKD. TIMP-2, tissue inhibitor of metalloproteinases-2; IGFBP7, insulin-like growth factor binding protein-7; L-FABP, L-type fatty acid binding protein; AKI, acute kidney injury; CKD, chronic kidney disease.

also demonstrated that habitual aerobic exercise increased physical activity and maximal oxygen consumption, and decreased urinary L-FABP levels (39,40). Considering that urinary L-FABP may indicate renal hypoxia, it may also reflect the degree of the age-related nephrosclerosis and be useful for its monitoring. Furthermore, habitual aerobic exercise may improve renal hemodynamics and prevent the progression of age-related nephrosclerosis.

Urinary L-FABP in coronavirus disease 2019 (COVID-19)

Since 2019, COVID-19 induced by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has become a public health problem worldwide. SARS-CoV-2 infects human cells via the angiotensin-converting enzyme 2 (ACE2) expressed in different cells, such as alveolar type II cells in the lung, renal proximal tubule cells, cardiomyocytes, epithelial cells of the ileum and esophagus, urothelial cells of the bladder, and vascular endothelial cells (62). Also, it induces systemic inflammation with release of various inflammatory cytokines, leading to a cytokine storm which causes damage to multiple organs (63). In addition, injury of endothelial cells increases the risk of thrombosis, such as cerebral infarction and myocardial infarction (64). Because the degree of organ damage or thrombosis is strongly associated with mortality, early detection of patients at high risk is needed to determine the treatment against COVID-19. A study evaluated the levels of urinary L-FABP in patients with COVID-19 (n=123) using a POC assay kit by 48 h after admission. The levels of urinary L-FABP were significantly higher levels in patients with a primary event (i.e., death, cerebral infarction, myocardial infarction, and stroke) than those without an event (41). Another report (n=49) also indicated that patients with high levels of urinary L-FABP, which were measured using the POC assay kit for 72 h after admission, could easily develop severe disease (42). Urinary L-FABP may be useful for the early determination of COVID-19 patients at high risk of critical illness.

Urinary L-FABP may be useful in various disease because renal hypoxia may be induced in different situation in addition to kidney disease (*Table 2*).

Conclusions

Tubular markers may reflect various renal and systemic pathological conditions. While urinary [TIMP-2]*[IGFBP7] may be useful for predicting the severity of AKI related to cardiac surgery, urinary L-FABP cloud improve management for patients with kidney diseases, such as AKI, AKI to CKD, and CKD (*Figure 1*). Furthermore, urinary L-FABP may predict the progression of age-related nephrosclerosis and COVID-19. Early utilization of an accurate marker may provide beneficial effects on the

prognosis of kidney disease and patient survival.

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Footnote

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